UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/913,756	01/05/2002	Rita Chiari	L0461/7121	5298

23628 7590 02/09/2005

WOLF GREENFIELD & SACKS, PC
FEDERAL RESERVE PLAZA
600 ATLANTIC AVENUE
BOSTON, MA 02210-2211

EXAMINER	
VANDERVEGT, FRANCOIS P	
ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 02/09/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/913,756	CHIARI ET AL.	
	Examiner	Art Unit	
	F. Pierre VanderVegt	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 November 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4,5,7,9,10,15,21,52,54 and 65-76* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4,5,7,9,10,15,21,52,54 and 65-76* is/are rejected.

7)☒ Claim(s) *2* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *01062005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This application is a rule 371 continuation of PCT Serial Number PCT/US00/04326, which claims the benefit of the filing date of provisional applications 60/160,374 and 60/179,570.

Claims 3, 6, 8, 11-14, 16-20, 22-51, 53, and 55-64 have been canceled.

New claims 65-76 have been added.

Claims 1, 2, 4, 5, 7, 9, 10, 15, 21, 52, 54 and 65-76 are currently pending and are the subject of examination in the present Office Action.

1. **In view of Applicant's amendment filed November 15, 2004 the following grounds of rejection are maintained.**

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 1, 4, 5, 7, 9, 10, 15, 21, 52, 54 and 65-76 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

It was previously stated: "The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. (See Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001, especially page 1106 3rd column). A "representative number of species" means that the species that are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. MPEP 2163 II.A.3a.ii.

Claims 1-4 broadly recite functional variants of the EphA3 HLA class II-binding peptides defined by SEQ ID NOs: 51, 52, 53, 54 and 62 as fragments of SEQ ID NOs: 3, 5, and 7, including variants comprising an amino acid deletion, addition or substitution. Thus Applicant has disclosed only a limited number of variants. The specification does not disclose any variants comprising sequence changes within or adjacent to the core sequence that can bind to HLA class II. The specification also does not disclose which residues of the core sequence are required for binding, i.e., cannot be changed and maintain

functional HLA class II binding, nor does it disclose where within that core sequence amino acid residues can be added, which residues can be changed or deleted or what type of change can actually be tolerated. It does not appear based upon the limited disclosure that Applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the limited number of species disclosed and the extensive variation permitted within the genus of "EphA3 HLA class II-binding peptides."

Consequently, Applicant was not in possession of the instant claimed invention. See Regents of the University of California v. Eli Lilly and Co. 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). Adequate written description of genetic material "'requires a precise definition, such as by structure, formula, chemical name, or physical properties,' not a mere wish or plan for obtaining the claimed chemical invention." Id. 43 USPQ2d at 1404 (quoting Fiers, 984 F.2d at 1171, 25 USPQ2d at 1606). The disclosure must allow one skilled in the art to visualize or recognize the identity of the subject matter of the claim. Id. 43 USPQ2d at 1406. A description of what the genetic material does, rather than of what it is, does not suffice. Id.

While the instant claims are drawn to peptides and not to nucleic acids, the cited case law is relevant because there is limited disclosure of the structure, formula, or physical properties of a "functional variant" and there is only a disclosure of what the "functional variant" does (bind HLA class II), rather than of what it is.

Applicant's arguments filed November 15, 2004 have been fully considered but they are not persuasive.

Applicant has amended base claim 1 to recite a functional variant of a fragment of SEQ ID NO: 3, 5 or 7 comprising 2 or fewer amino acid substitutions.

Applicant argues that the claimed functional variant is adequately described in the specification because the specification comprises a working example of a functional variant (SEQ ID NO: 62) that comprises two amino acid substitutions versus SEQ ID NO: 53. However, demonstrating possession of a single species does not necessarily extend to the entire genus. In the present case, the claim is drawn to functional variants of HLA class II binding fragments of SEQ ID NO: 3, 5 or 7. The claim is not limited by the HLA class II molecule that is bound by the variant. The specification does not disclose all of the HLA class II binding peptides comprised within the sequence of SEQ ID NO: 3, 5 or 7. Nor does the specification disclose any HLA class I binding fragments of SEQ ID NO: 3, 5 or 7 [claims 9, 10]. The only binding peptide disclosed as a fragment of SEQ ID NO: 3, 5, or 7 is SEQ ID NO: 53 and that fragment only binds a single HLA class II haplotype. SEQ ID NO: 3 is 983 amino acids in length. Assuming HLA class II binding fragments having the same 12 amino acid length as SEQ ID NO: 62, there are 972 contiguous 12-mer peptides representing potential HLA class II binding peptides. Functional variants comprising a single amino acid substitution represent 19 variants of each of those fragments, or 18,468 potential functional variant HLA class II binding peptides. Functional variants comprising two amino acid substitutions represent a further 19^2 variants of each of those fragments, or 350,892 potential functional variant HLA class II binding peptides. Combined, Applicant's working

example of the single variant of SEQ ID NO: 62 is alleged to represent 369,360 potential functional variant HLA class II binding peptides of SEQ ID NO: 3. it is respectfully submitted that the only functional variant of a functional variant HLA class II binding peptide of SEQ ID NO: 3, 5 or 7 that is adequately represented by SEQ ID NO: 62 is SEQ ID NO: 62 itself because that is the only sequence for which it can support two amino acid changes that result in a peptide capable of binding HLA class II.

3. Claims 1, 4, 5, 7, 10, 15, 21, 52, 54 and 65-76 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated EphA3 HLA class II binding peptide, wherein said peptide consists of a fragment of the amino acid sequence of SEQ ID NO: 3, 5 or 7, and wherein said fragment comprises SEQ ID NOs: 51, 52, 53, 54 and 62, does not reasonably provide enablement for an isolated EphA3 HLA class II binding peptide that consists of a functional variant of a fragment of SEQ ID NOs: 3, 5, or 7or a functional variant of SEQ ID NOs: 51, 52, 53, 54 or 62 comprising an amino acid addition, deletion or substitution. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

It was previously stated: "Claims 1 and 2 recite EphA3 HLA class II-binding peptides defined as fragments of SEQ ID NOs: 3, 5, and 7 and claims 3 and 4 more specifically recite the fragments as SEQ ID NOs: 51, 52, 53, 54 and 62. Claims 1-4 broadly recite functional variants of the recited peptides including variants comprising an amino acid deletion, addition or substitution.

The specification does not identify the residues of the peptides that are important for interaction with the HLA class II molecule or with the responding T cell and therefore provides no guidance in regard to the residues that are especially recalcitrant to change and maintain the functional nature of the peptide. Further, there is no disclosure of the non-interaction residues that are not amenable to change. The specification defines a functional variant at the paragraph bridging pages 12 and 13 as "a peptide which contains one or more modifications to the primary amino acid sequence of a HLA class I or class II binding peptide and retains the HLA class I or class II binding properties disclosed herein." Smilek (Proc. Nat. Acad. Sci. (USA) [1991] 88:9633-9637; U1 on form PTO-892) discloses a myelin basic protein peptide with an amino acid change that alters the function of the peptide drastically. Smilek discloses that replacing the lysine at position 4 of the 11-mer with an alanine increases the MHC class II binding of the peptide at least 10 fold, but changes the *in vivo* "function" of the peptide from being encephalogenic to preventative for EAE induction. Accordingly, greater guidance is required from the specification for the artisan to be able to make and use functional derivatives where amino acid residues are subject to "substitution."

Further, the scope of the claims encompasses the addition or deletion of unspecified amino acid residues to the peptide fragments of SEQ ID NOs: 3, 5 and 7. The skilled artisan can make fragments *limited* to *sub*sequences of SEQ ID NO: 3, 5 or 7 and encompassing SEQ ID NO51, 52, 53, 54 or 62 without undue experimentation. However, before the skilled artisan can make polypeptides comprising with additional flanking amino acid residues that are not part of SEQ ID NO: 3, 5, or 7, guidance is required with respect to the identity of those flanking residues. In the instant case however, the

specification does not appear to provide this needed guidance. In addition, guidance is required to add intervening amino acid residues within the epitope or to delete intervening amino acid residues within the epitope, as the additional residues or the shortened distance between critical residues would be predicted to interfere with the structure of the epitope. Therefore the scope of the instant claims encompassing functional variants having "amino acid additions" or "amino acid deletions" does not appear to be commensurate with the enablement provided by the instant disclosure.

In view of the breadth of the claims, the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, and the lack of sufficient guidance in the specification, it would take undue trials and errors to make and use the claimed invention.

Applicant argues that the claims are fully enabled because the working example of SEQ ID NO: 62 demonstrates that a variant peptide of SEQ ID NO: 53 can have 2 amino acid changes and still bind to HLA class II. Applicant further asserts that it would not require undue experimentation to alter any of the other 7 amino acid residues of SEQ ID NO: 53 because peptide synthesis is entirely routine in the art. This is not convincing. First of all, the ability to synthesize a peptide has nothing to do with the determination of the ability of that peptide to bind HLA class II. second, SEQ ID NO: 62 is not representative of two amino acid substitutions of SEQ ID NO: 53. The 12-mer of SEQ ID NO: 62 includes 3 additional amino acids N-terminal to the Phe in position 1 of the 9-mer of SEQ ID NO: 53 and the substitution of ONLY the Cys residue in position 8 of SEQ ID NO: 53 for a Ser residue in position 11 of SEQ ID NO: 62. Accordingly, Applicant's asserted basis for support of enablement is not commensurate with the disclosure in the specification.

Furthermore, this single amino acid residue substitution demonstrates only that position 8 of SEQ ID NO: 53 can be substituted with a serine residue. The working example still falls short of showing which residues are especially recalcitrant to change, nor is there disclosure of the non-interaction residues that are not amenable to change.

4. **The following new ground of rejection has been necessitated by Applicant's amendment.**

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claim 4 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 4 is ambiguous and unclear because it is written as an improper Markush group. The word --and-- should be inserted before the recitation of "SEQ ID NO: 62" in order to properly close the group.

Claim 4 recites the limitation "the fragment comprises an amino acid sequence selected from the group consisting of SEQ ID NO:51, SEQ ID NO:54, SEQ ID NO:62" in lines 2-3. There is no antecedent basis for this limitation in the claim. SEQ ID NOs: 51, 54 and 62 each comprise substitutions and therefore do not constitute fragments of SEQ ID NO: 3, 5 or 7 as recited in the base claim. SEQ ID NOs: 51, 54 and 62 instead represent functional variants of fragments.

Conclusion

6. Claim 2 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

7. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to F. Pierre VanderVegt whose telephone number is (571) 272-0852. The examiner can normally be reached on M-Th 6:30-4:00; Alternate Fridays 6:30-3:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

F. Pierre VanderVegt, Ph.D.
Patent Examiner
February 3, 2005

PATRICK J. NOLAN, PH.D.
PRIMARY EXAMINER
2/7/05